

Effectiveness of 3rd generation cephalosporin compare to 3rd generation cephalosporin - macrolides for *community acquired pneumonia* patients in PKU Muhammadiyah Yogyakarta Hospital

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ABSTRACT

Pneumonia is a lung infection caused by bacteria with high fever symptoms accompanied by cough with phlegm, shortness of breath. According to Risesdas 2013 results, the prevalence of pneumonia based on diagnosis at Yogyakarta Special Region is 1.7% and 4.6%. The researcher has founds 172 adult patients diagnosed pneumonia during 2011-2016 in PKU Muhammadiyah Yogyakarta hospital. This study aims to determine the level of effectiveness between 3rd generation cephalosporins with 3rd generation cephalosporins and macrolides on the outcome of adult patients with pneumonia in PKU Muhammadiyah Yogyakarta hospital period 2015-2017. It was a retrospective cohort study with an affordable population. There were two groups of 3rd generation cephalosporins (n = 24) compared to the 3rd generation cephalosporins and macrolide (n = 13) measured results in the form of body temperature, shortness of breath, leukocyte count, and length of hospitalization using univariate and bivariate analyzes. Based on the results of the study, 70.3% was dominated by men, and 51.4% was dominated by the age group > 59 years. Both of groups showed a significant difference to the temperature where $p=0.001$ with difference of temperature decrease 0.79 ± 1.06 °C for single group while $p=0.049$ with difference of temperature decrease 0.65 ± 1.07 °C for combination group; as well as against leukocyte, both of groups had a value of $p=0.001$ where difference of leucocyte decrease was 4.80 ± 3.92 $10^3/\text{mm}^3$ for single group and 5.43 ± 4.27 $10^3/\text{mm}^3$ combination group. While both of group showed no significant difference for shortness of breath $p=0.638$ with OR (95% CI) 2.4 (0.23 – 24.06) and $p=0.435$ for hospitalization, in single group was 5.88 ± 3.261 days while in combination group was 5.00 ± 1.826 , this shows that the combination group had an average length of hospitalization of 0.88 days faster than the single group. The effectiveness between two groups showed a significant difference with $p<0.05$ on body temperature and leukocyte count. While both groups did not show a significant difference with $p>0.05$ to shortness of breath and length of stay.

Keywords: antibiotics, therapy effectiveness, *Community Acquired Pneumonia* (CAP)

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INTRODUCTION

Pneumonia is a lung infection caused by bacteria with high fever symptoms accompanied by cough with phlegm, rapid breathing (breathing frequency > 50 times per minute), shortness of breath, and other symptoms such as headache, anxiety and decreased appetite (Anonim, 2013). Most pneumonia is caused by microorganisms such as bacteria or viruses and a small part is caused by aspiration and radiation. In developing countries, pneumonia is caused by bacteria (Kamal, 2015). Common causes of pneumonia are typical bacteria, especially *Streptococcus pneumonia*, *Haemophilus influenza*, and *Staphylococcus aureus*. Pneumonia bacterial is generally responsive to treatment with beta-lactams, whereas those unresponsive to the beta-lactam group called atypical pneumonia (Said, 2010).

As big as 1% of adults have CAP annually. The diagnosis of adult patients with lower-respiratory tract infections is 5-12%, and 22-24% of these diagnoses are hospitalized in the UK, where mortality ranges from 5% to 14%. As big as 1.2% to 10% of adult patients with pneumonia are hospitalized for intensive care, and for these patients the risk of death is greater than 30% (Woodhead, et al., 2014).

Period prevalence in 2013 is 1.8 percent and 4.5 percent. The five provinces with the highest incidence and prevalence of pneumonia for all ages were East Nusa Tenggara at 4.6% and 10.3%, Papua 2.6% and 8.2%, Central Sulawesi 3.5% and 7.2% 3.1% and 6.1%, and South Sulawesi 2.8% and 6.8% (Anonim, 2013). While the Special Region of Yogyakarta (DIY) is 1.7% and 4.6% (Anonim, 2013). Based on the population age group, the prevalence of high pneumonia occurs in the age group 1 - 4 years, then begins to increase at age 45 - 54 years and continues to increase in the next age group (Anonim, 2013).

Preliminary study on the patients with pneumonia (J18.9) conducted by researchers retrospectively in 2011 - 2016 in hospital PKU Muhammadiyah Yogyakarta as many as 172 adult inpatients. A total of 110 is dominated by men while 62 are female patients. The study is expected to provide information on the use of antibiotics to the outpatient of pneumonia therapy of adult patients at the hospital inpatient installation PKU Muhammadiyah Yogyakarta and increase the active role of pharmaceutical practitioners in monitoring and evaluating the use of antibiotics to the outcome of pneumonia patient therapy.

MATERIAL AND METHODS

Instruments and samples

This study used a retrospective cohort design. The data were taken from medical record at hospital medical unit of PKU Muhammadiyah Yogyakarta period 2015 until 2017 with the number of affordable population as many as 37 CAP patients with total sampling method. Supporting data in this research are name, age, gender, antibiotic usage data (name, dose, frequency, duration), diagnostic data from doctor in charge including examination of body temperature, shortness of breath, leukocyte count, and length of stay.

The data were taken according to the inclusion criteria which included (1) ≥ 18 patients with diagnosed community acquired pneumonia ICD (J1.9) who was admitted to hospital PKU Muhammadiyah Yogyakarta. (2) patients receiving either a 3rd-generation or single-cephalosporin antibiotic therapy combination with macrolide for at least 72 hours (Bradley, et al., 2011). (3) CAP patients with leukocytosis ($>10/\text{mm}^3$) adjusted the standard laboratory values of PKU Muhammadiyah Yogyakarta hospital. While for the exclusion criteria are: (1) the patient is declared to be forced or died (before 72 hours / three days of therapy with cephalosporin 3rd generation single or combination with macrolide) in the hospital treatment

PKU Muhammadiyah Yogyakarta. (2) patients with other infections. (3) patients with immunosuppressed disorders.

Research variables

Independent variable

Independent variables in this research are type of antibiotics, i.e. 3rd generation cephalosporin antibiotic single or combination 3rd cephalosporin with macrolide.

Dependent variable

Dependent variable in this study which will be examined the results are leukocyte, body temperature, shortness of breath, and length of stay.

Confounding variable

The confounding variables in this study are patient accompanying diseases and the presence of drug related problems that can interfere with the effectiveness of treatment.

Data Analysis

Characteristics test of each antibiotic using univariate analysis. The first requirement for the comparative test of antibiotics on the outcome of therapy is to test the data normality first to ensure the value of each data distribution of each group by Shapiro Wilk method because the sample is below 50 data.

Results of temperature normality test in 3rd generation cephalosporin is $p = 0.254$ while combination of 3rd generation cephalosporin and macrolide that is $p = 0.311$. The test indicates that the distribution of data is normal with $p > 0.05$ so that this comparative statistic test using parametric test with T-test paired method for interval data with $p > 0.05$.

Results of shortness of breath normality test in both of groups is $p = 0.001$. The test indicates that the distribution of data is abnormal with $p < 0.05$ so this comparative statistic test using non parametric test with Fisher's method for nominal data with $p < 0.05$.

Results of leucocyte count normality test in 3rd generation cephalosporin is $p = 0.982$ while combination groups is $p = 0.163$. The test indicates that the distribution of data is normal with $p > 0.05$ so this comparative statistic test using parametric test with T-test paired method for interval data with $p > 0.05$.

Results of length of stay normality test in 3rd generation cephalosporin is $p = 0.001$ while combination groups is $p = 0.039$. The test indicates that the distribution of data is abnormal with $p < 0.05$ so this comparative statistic test using non parametric test with Mann-Whitney method for interval data with $p < 0.05$ (Ethical Number: 011710140).

RESULTS AND DISCUSSION

Patient characteristics

Subjects in this study included the gender and age of adult CAP patients. A total of 37 divided into two groups namely 3rd generation cephalosporins as many as 24 patients, and a combination of cephalosporins 3rd generation and macrolide as many as 13 patients. Characteristics of patients receiving antibiotics can be seen at [Table I](#).

Table I. Characteristics of CAP patients admitted to hospital at PKU Muhammadiyah Yogyakarta who received antibiotics

Characteristics	Total (%)	Mean \pm SD	3rd generation cephalosporins n (%)	3rd generation cephalosporins & macrolide n (%)	P
Sex					
Male	26 (70.3)	-	18 (69.2)	8 (30.8)	0.399
Female	11 (29.7)		6 (54.5)	5 (45.5)	
Ages					
18-59 years old	18 (48.6)	57.49 \pm 15.12	12 (66.7)	6 (33.3)	0.826
> 59 years old	19 (51.4)		12 (63.2)	7 (36.8)	

Based on sex, 70.3% is dominated by men compared to women who only 29.7%. Similar to previous research of [Hariri *et al.* \(2017\)](#) male patients with adult CAP inclusion were 55% greater than female patients at 45%. Similarly, research of [Sajinadiyasa, *et al.* \(2011\)](#) where the largest population is men with 52.72% compared to women who only 47, 27%. And 64% of men dominate the adult CAP population than women who are only 36% ([Zhong, *et al.*, 2014](#)). The greater risk of community pneumonia in men is greater because of the greater incidence of cigarette smoking for adult males, it also increases the risk of lung disease such as bronchitis or community pneumonia ([Elfidasari, *et al.*, 2013](#)).

Based on age in this study shows that 51.4% is dominated by age group above 59 years, while the remaining is dominated by age group of 18 - 59 years of 48.6% with an average yield of 57.49 years. Similar to subsequent studies, patients over the age of 60 years also dominate the CAP subject of inpatients ([Pahriyani, *et al.*, 2015](#)). But contrast to research [Sajinadiyasa, *et al.* \(2011\)](#) of 53.3% is more dominated by the age group span of under 60 years and only 46.7% in the age group above 60 years. According to [Prince \(2006\)](#), immunity in maintaining the body will decline with age that begins when it has stepped on 50 years and above, it is possible that the number of patients over 50 years affected by community pneumonia. It is above shows that there is no significant difference between men and women, as well as between the ages of 18-59 with > 59 years.

Difference effectiveness of the antibiotics to temperature outcome

This aims to determine differences in clinical changes of CAP patients after 3rd generation cephalosporins compared to combination of 3rd generation cephalosporins and macrolides at the hospitalization of PKU Muhammadiyah Yogyakarta hospital. The clinical parameters of the patients measured before and after antibiotics are temperature which is an indication of infection in the body and as a target for the patient's clinical condition ([Bradley, *et al.*, 2011](#)).

CAP patient temperature measurements were performed when the patient was admitted to hospital with CAP diagnosis and had not received antibiotics and further temperature measurements were performed at the time of antibiotic therapy over 72 hours.

Table. II Descriptive analysis and 3rd generation cephalosporins effectivity differences compared to 3rd generation cephalosporins and macrolides to temperature outcomes

Groups	Mean \pm SD	Difference \pm SD	Range	P	P
The 3 rd generation cephalosporin (n = 23)					
Temperature before therapy	37.2 \pm 0.87	0.79 \pm 1.06	0.9 (1.24 – 0.24)	0.001*	
Temperature after therapy	36.4 \pm 0.99				0.001*
The 3 rd generation cephalosporin and macrolide (n = 14)					
Temperature before therapy	37.1 \pm 0.97	0.65 \pm 1.07	1.30 (1.30-0.003)	0.049*	
Temperature after therapy	36.4 \pm 0.35				

*t-test paired

[Table.II](#) shows two descriptives and t-test paired analyzes. Descriptive analysis showed that each 3rd generation cephalosporins (single) and 3rd generation cephalosporin and macrolide (combination) had an average difference and the difference in decreasing CAP patient temperature. Difference in temperature of single group had 0.79 °c with standard 1.06 intake while the difference in temperature drop in combination groups had 0.65 °c with standard deviation 1.30. Judging from the difference in temperature decrease for both groups above, single group was higher in decreasing temperature compared to the combination groups. As for the range of temperature drop, the combination groups with a range of 1.30 °c is greater than the single group with a range of 0.9 °c. The

value is obtained from the maximum value of CAP patient temperature minus the minimum value of CAP patient's body temperature.

The result paired T-test analysis on single group with $p = 0.001$ showed that there was a significant difference between patient's temperature before and after single treatment because $p < 0.05$ similarly in combination groups with $p = 0.049$ showed that there was a significant difference between body temperature of patients before and after combination treatment because $p < 0.05$. It is above shows that there is a significant difference between the use of 3rd generation cephalosporins and 3rd generation cephalosporins and macrolides againts temperature before and after therapy.

Difference effectiveness of the antibiotic to shortness of breath outcomes

This aims to know the difference of 3rd generation cephalosporin compared to 3rd generation cephalosporin and macrolide to shortness of breath of adult CAP patient at hospitalization of PKU Muhammadiyah Yogyakarta hospital. Parameters measured at the time the patient has been out of the hospital the patient is still complaining of shortness of breath or not. Shortness of breath is an indication of the presence of infection in the body and as a target stability of the patient's clinical condition (Bradley, *et al.*, 2011).

Table III. Differences in effectiveness of 3rd generation cephalosporins compared to 3rd generation cephalosporins and macrolides againts shortness of breath of adult CAP

Groups	Shortness Of Breath		<i>P</i> ($p < 0.05$)
	Yes (%)	No (%)	
3 rd generation cephalosporins	4 (16.7)	20 (83.3)	0638 *
3 rd generation cephalosporins and macrolide	1 (7.7)	12 (92.3)	
Total (%)	5 (13.5)	32 (86.5)	37 (100)
*Fisher's			

Table III shows results of fisher's test ($p = 0.638$), the results show $p > 0.05$ there is no significant difference between the 3rd generation cephalosporin versus 3rd generation cephalosporins and macrolides againts shortness of breath therapy in adult CAP patients who are hospitalized.

Difference effectiveness of the antibiotic to leucocyte outcome

Leukocyte measurements were performed twice when patient was admitted to the hospital with CAP diagnosis before receiving antibiotic therapy and 72 hours after patient received antibiotic therapy. For statistical analysis test results can be seen in Table IV below.

Table IV. Descriptive analysis and difference in effectiveness of 3rd generation cephalosporins compared to 3rd generation cephalosporins and macrolides against leukocyte

Groups	Mean \pm SD	Difference \pm SD	Range	P	P
3 rd generation cephalosporin (n = 23)					
Before therapy	14.2 \pm 2.92	4.80 \pm 3.92	3.31 (6.45 – 3.14)	0.001*	
After therapy	9.40 \pm 2.74				0.001*
3 rd generation cephalosporin and makrolida (n = 14)					
Before therapy	16.48 \pm 4.04	5.43 \pm 4.27	5.17 (8.02 – 2.85)	0.001*	
After therapy	11 \pm 3.52				

*t-test paired

Table IV. shows that the leukocyte difference decrease on combination with 3rd generation cephalosporins and macrolides was greater with a decrease of $5.43 \times 10^3 / \text{mm}^3$ and deviation standard of 4.27 compared to 3rd generation cephalosporins was only $4.8 \times 10^3 / \text{mm}^3$ and deviation standard 4.27. Furthermore, for the decrease range of leukocyte numbers, 3rd generation cephalosporins and macrolides with a range of $5.17 \times 10^3 / \text{mm}^3$ is greater than the 3rd generation cephalosporin with a range of $3.31 \times 10^3 / \text{mm}^3$. The range value is obtained from maximum leukocyte value minus leukocyte value of the CAP patient.

The result of paired t-test for 3rd generation cephalosporin with value ($p = 0,001$) while the combination group of 3rd generation cephalosporin and macrolide with value ($p = 0,001$) statistically showed a significant difference between the use of 3rd generation cephalosporin and a combination of 3rd generation cephalosporins and macrolides against leukocyte reduction in CAP patients. It is above shows that there is a significant difference between the use of 3rd generation cephalosporins and 3rd generation cephalosporins and macrolides against leukocyte before and after therapy.

In a fact in the use of combination of 3rd generation cephalosporins and macrolides, which macrolides can help decrease the production of interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF- α) in pneumonia patients (Takizawa, *et al.*, 1997). Gram-negative bacteria in their cell membrane structure are composed of lipopolysaccharide endotoxin (LPS). When these bacteria infect the body, non-specific defense systems such as macrophages will recognize LPS from gram-negative bacteria, the presence of bonds between macrophages with LPS will cause macrophages to express a number of proinflammatory cytokines IL-8 and TNF- α . Activation of these cytokines in excessive amounts automatically leads to worse patient prognosis such as Systemic Inflammatory response syndrome (SIRS) as well as sepsis (Baratawidjaja, *et al.*, 2014).

Difference effectiveness of the antibiotic to length of stay

This aims to determine the difference of 3rd generation cephalosporins compared to 3rd generation cephalosporins and macrolides to length of stay of adult CAP patients at the hospitalization of PKU Muhammadiyah Yogyakarta hospital. Parameters were measured using a count of days during which patients were admitted to hospital.

Table.V Differences in effectiveness of 3rd generation cephalosporins compared to 3rd generation cephalosporins and macrolides on the length of stay in adult CAP patients

Length of stay	Antibiotics		<i>P</i>
	3 rd generation cephalosporins	3 rd generation cephalosporins and macrolides	
<i>The Mean ± SD</i>	5.88 ± 3.261	5.00 ± 1.826	
<i>Median</i>	5.00	4.00	0.435*
<i>Range</i>	15	6	

*Mann-whitney

Table.V shows a Mann-Whitney analysis with a value ($p = 0.435$), because $p > 0.05$ its shows that there is no significant difference between the use of a 3rd generation cephalosporin single antibiotic compared to a combination of 3rd generation cephalosporins and macrolides the long-term outcome of hospitalization in adult CAP patients statistically. However, mean \pm SD results indicate that the use of 3rd generation cephalosporins with macrolides is 0.88 days longer in hospital than a 3rd generation cephalosporins although not significantly different.

This is similar with research of [Sajinadiyasa, et. al. \(2011\)](#) used a inpaired T-test of the Mann-Whitney method where the average length of stay of combined antibiotic use had 8.58 days with a deviation standard of 0.917 (8.58 ± 0.917) while the use of a single antibiotic had 14, 80 days with deviation standard of 4.258 (14.80 ± 4.258), its indicated that combination antibiotic usage had average length of stay faster than single antibiotic with p value = 0.075 ($p > 0.05$) which mean there was not significant difference between both of these antibiotics. Similar with [Trowbridge, et. al. \(2002\)](#) where the use of combination 3rd generation cephalosporin and macrolides (azithromycin) had a 4.6 day treatment time with a deviation standard of 0.34 (4.6 ± 0.46) while 3rd generation cephalosporins(ceftriaxon) had a long treatment time of 6.3 days with a deviation standard of 0.53 (6.3 ± 0.53) having a significant relationship with $p < 0.05$. This possibility is triggered by a lack of patient suggestion to heal on the use of this single antibiotic.

The treatment between combination 3rd generation cephalosporins and macrolides was more effective in reducing mortality and length of stay than a single 3rd generation cephalosporin for CAP patients with $p = 0.03$ 97% CI ([Caballero and Rello, 2011](#)). Administration of macrolides in CAP patients during the first 24 hours will inhibit the occurrence of inflammation in the early stages of the disease. This macrolides can shortens the length of stay admitted to the hospital after 24 hours. This proves that macrolides can inhibit the production of interleukins and may reduce the proinflammatory agent resulting from bacterial production ([Culic, O., et al., 2002](#)).

Treatments with beta-lactamase and macrolides may reduce risk of death higher than 3rd generation cephalosporins alone, but both in a double-blind Random Controlled Trials study where treatments combination beta-lactamase and macrolides and beta lactamase alone is needed for CAP patients ([Niet, et al., 2014](#)). In contrast to a study conducted by Health Quality Ontario (2013) there was no significant difference in mortality reduction or treatment failure in inpatient CAP patients receiving either combination or single antibiotic therapy.

LIMITATIONS OF THE RESEARCH

The researchers excluded a large number of subjects due to the lack of re-leukocyte tests in patients, which resulted in the number of patients taken as respondents too few. The subject of CAP is considered equal in terms of severity (*mild, moderate, severe*).

CONCLUSION

Comparison of therapeutic efficacy of 3rd generation cephalosporins alone againsts 3rd generation cephalosporins and macrolides showed significant difference on temperature and leukocyte with $p < 0,05$. While the effectiveness of 3rd generation cephalosporins alone againsts 3rd generation cephalosporins and macrolides showed no significant difference shortness of breath and length of stay with $p > 0,05$.

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